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The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina:

A meta-analysis focused on post-test disease probability

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Abbreviations

CAD Coronary artery disease

CCTA Coronary computed tomography angiography

CMR Cardiovascular magnetic resonance

ICA Invasive coronary angiography

IVUS Intravascular ultrasound

OCT Optical coherence tomography

PET Positron emission tomography

PTP Pre-test probability

QCA Quantitative coronary angiography

SPECT Single photon emission computed tomography

ABSTRACT

Aims

To determine the ranges of pre-test probability (PTP) of CAD in which stress ECG, stress echocardiography, coronary computed tomography angiography (CCTA), single-photon emission computed tomography (SPECT), positron emission tomography (PET) and cardiac magnetic resonance (CMR) can reclassify patients into a post-test probability that defines (>85%) or excludes (<15%) anatomically (defined by visual evaluation of invasive coronary angiography [ICA]) and functionally (defined by a fractional flow reserve [FFR] ≤0.80) significant CAD.

Methods and Results

A broad search in electronic databases until August 2017 was performed. Studies on the aforementioned techniques in >100 patients with stable CAD that utilized either ICA or ICA with FFR measurement as reference, were included. Study-level data was pooled using a hierarchical bivariate random-effects model and likelihood ratios were obtained for each technique. The PTP ranges for each technique to rule-in or rule-out significant CAD were defined. 28,664 patients from 132 studies that used ICA as reference and 4,131 from 23 studies using FFR, were analyzed.

Stress ECG can rule-in and rule-out anatomically significant CAD only when PTP is ≥80% [76, 83] and ≤19% [15, 25], respectively. CCTA is able to rule-in anatomic CAD at a PTP ≥58% [45, 70] and rule-out at a PTP ≤80% [65, 94]. The corresponding PTP values for functionally significant CAD were ≥75% [67, 83] and ≤57% [40, 72] for CCTA, and ≥71% [59, 81] and ≤27 [24, 31] for ICA, demonstrating poorer performance of anatomic imaging against FFR. In contrast, functional imaging techniques (PET, stress CMR and SPECT) are able to rule-in functionally significant CAD when PTP is ≥46-59% and rule-out when PTP is ≤34-57%.

Conclusion

The various diagnostic modalities have different optimal performance ranges for the detection of anatomically and functionally significant CAD. Stress ECG appears to have very limited diagnostic power. The selection of a diagnostic technique for any given patient to rule-in or rule-out CAD should be based on the optimal PTP range for each test and on the basis of the assumed reference standard.

Keywords: Stable coronary artery disease, non-invasive imaging, pre-test probability, post-test probability, likelihood ratio

INTRODUCTION

Accurate detection of coronary artery disease (CAD) remains paramount in the practice of cardiology. Traditionally, the characterization of "significant" CAD has relied upon visual evaluation of coronary artery stenosis during invasive coronary angiography (ICA). However, the severity of angiographic stenosis does not unequivocally reflect its functional significance.(1) Recently, the invasive assessment of fractional flow reserve (FFR) has been adopted to identify functionally significant coronary artery stenoses.(2) Yet, FFR evaluation is not without limitations as diffuse CAD and hemodynamic conditions have shown an influence on its estimation, it is inherently invasive and costly, and it still does not represent the most common practice in invasive evaluation of CAD.(3)

Stable CAD is understood as the condition characterized by episodes of inducible and reversible ischemia commonly associated with transient chest discomfort. The current European and American guidelines on the management of stable CAD(2,4) recommend that patients with an intermediate pre-test probability (PTP) (ranging from 15 to 85%) of significant CAD should undergo non-invasive evaluation(5,6). In subjects whose probability of a significant coronary artery narrowing is low (<15%), routine testing is not recommended. On the other hand, patients with a high probability (>85%) of the disease calls for direct therapeutic interventions.

In the group of patients with intermediate PTP of significant CAD, the current recommendations for the selection of the optimal non-invasive technique are broad and do not assign preference of one modality over another. Certain techniques are broadly available because of their relative low technical and personnel demands (such as stress ECG) or good availability (stress echocardiography, coronary computed tomography angiography [CCTA], and single-photon emission computed tomography [SPECT]), while others, like positron emission tomography (PET) and stress cardiac magnetic resonance (CMR), although

powerful, are much less available and their applicability is still limited by infrastructural and capacity requirements (7).

It is expected that each technique has a particular range of PTP of significant CAD where the usefulness of its application is maximized. The performance of non-invasive techniques is generally reported in terms of sensitivity and specificity. Nevertheless, these numbers cannot be readily utilized in the clinical decision-making process. They can however be used to derive positive and negative likelihood ratios (LR+ and LR-), which constitute readily useful parameters of a test's accuracy that facilitate the selection of a diagnostic test for individual patients.(8) Given a PTP of significant CAD and the performance of a particular test by means of its LR's, one can assess the post-test probability of significant CAD after performing such test. Using this approach, one can estimate the range of PTP when a positive or negative test result can confidently rule-in (if the post-test probability goes beyond 85%) or rule-out (if the post-test probability drops below 15%) the disease.

As currently both anatomical (ICA) and functional (FFR) reference standards are utilized, it is rational to consider evidence using both standards.(9) The anatomical standard has been used in most of the studies available today and there is a massive amount of evidence, although functional information has gained increasing interest. It can be expected that some tests demonstrate better agreement with ICA while others with FFR. Therefore, integration of all available data may provide important clinical information for conscious selection of the tests.

The aim of the present systematic review and meta-analysis was to evaluate the diagnostic performance of stress ECG, stress echocardiography, CCTA, SPECT, PET, stress CMR, and ICA in the detection of anatomically and functionally significant CAD in order to determine the optimal range of PTP in the diagnostic application of each technique for ruling-in or ruling-out significant CAD.

METHODS

The present systematic review was conducted in accordance to the Preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA)(10) recommendations and the MOOSE checklist (see results and e-Table 1 in the supplement).(11)

Data Sources

We performed a systematic search for original studies published until August 2017 that reported on the diagnostic performance of stress ECG, stress echocardiography, CCTA, SPECT, PET, stress CMR, and ICA for the detection of significant CAD.

The search was performed in electronic databases (Medline, Embase, PubMed, Scopus, The Cochrane Library, Web of Science, ProQuest) using a broad strategy with a combination of MeSH terms and free text words sensitive to: identify studies concerning 1) the aforementioned diagnostic techniques, 2) diagnostic performance, 3) patients with intermediate pre-test probability of the condition, and 4) significant CAD. The search results were limited to the English language and to studies performed in humans. The full search string is reported in e-Table 2. Reference lists from relevant studies were scanned and cross-checked to identify potentially overlooked publications.

Study Selection and Quality Assessment

Studies were included according to the following eligibility criteria: 1) the study aimed to investigate stable CAD (not acute coronary syndromes), 2) either catheter-based X-ray angiography (ICA) or ICA with FFR evaluation were used as the reference standard for the diagnosis of stable CAD, 3) the reported data was explicit or sufficient to extract numbers for true and false positive and negative results, and 4) the study included a sample of at least 100 patients (for robustness). Selected studies were further divided according to the reference standard considered (ICA or FFR evaluation).

For each included study, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria were determined by two authors (LJ and HB). The QUADAS-2 tool assesses the study quality in different domains including patient selection, index test, reference standard, and flow of patients through the study considering the timing of the index test and reference standard. For each article, quality and applicability were assessed in the aforementioned domains as follows: “yes” if concern existed based on enough description in the report, “no” if there was no concern based on enough description in the report or “unclear” if there was inadequate or insufficient information reported in the article to make a judgment.

Data Extraction

Data were recorded according to the technique and reference standard utilized. The number of subjects, male to female patient proportion, age, type of stressor, tracer utilized (if any), stable CAD definition, and prevalence were extracted. The number of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), as well as derived diagnostic performance variables were recorded.

Study review, quality evaluation, and data extraction were performed in parallel by two authors (AS and HB). Any specific discrepancies were resolved by consensus. If necessary, a third reviewer (JK) was considered to reach convergence.

Reference Standard

Catheter-based ICA alone and ICA with FFR measurement were considered as the reference standards for the determination of anatomically significant and functionally significant CAD, respectively. Anatomic coronary narrowing >50% was considered as determinant of significant CAD and an FFR≤0.80 was considered as functionally significant CAD.

Data synthesis and statistical analysis

Hierarchical bivariate random-effects models were constructed to combine individual study-level data on the sensitivities and specificities across studies. This model takes the correlation between sensitivity and specificity into account, and is described in detail elsewhere.(12) The bivariate model used parametrization to render summary points for sensitivity and specificity with 95% confidence intervals [CI] for each of the imaging techniques. We used an unstructured covariance matrix allowing all variances and covariances to be distinct. We then derived summary estimates of the LR+ and LR- with their confidence intervals from the model estimates. For echocardiography and SPECT, more than one type of stressor was used. We compared if a model distinguishing by type of stressor had a better model fit than a model grouping all stressor techniques together. The analysis was performed separately for anatomically and functionally significant CAD (according to the reference standard used). We used the p-value from the likelihood ratio test to determine if the model with a covariate for the type of stressor fitted the data better than a model without such covariate. If the p-value was 0.05 or less, we depicted summary estimates for a specific type of stressor.

Utility of non-invasive approaches according to pre-test probability of stable CAD

Once the positive and negative LRs of each non-invasive diagnostic technique were obtained for both accepted reference standards, the ranges and in which every single technique allows to confidently rule-in CAD, rule-out CAD, or both were input into a color-coded graph. Additionally, we created a supplemental color-coded suggestion over the structure of the current ESC guidelines stable CAD PTP table to depict the suggested utility of each diagnostic technique at each level of risk based on age, sex, and type of symptoms.

RESULTS

Study Characteristics

The study selection flow chart is shown in Figure 1. Specific characteristics and the full reference for each selected study can be consulted in e-Table 3 in the Supplement. After eligibility assessment and technique subgroup characterization, 13 studies on stress ECG, 12 studies on exercise stress echocardiography, 30 on dobutamine stress echocardiography, 9 studies on CCTA, 28 studies on exercise & adenosine or dipyridamole stress SPECT, 13 on exercise stress SPECT, 3 studies on PET, and 11 on stress CMR were considered for the pooled analysis on anatomically significant CAD. On the other hand, 2 studies in ICA, 7 studies on CCTA, 5 on exercise stress SPECT, 4 on PET, and 5 on stress CMR were considered for the pooled analysis on functionally significant CAD.

Study Heterogeneity and Quality

Risk of bias in the included studies, as assessed with the QUADAS-2 score, showed important variation across diagnostic modalities. Overall, PET, CCTA, and stress CMR showed a low risk of bias and therefore, did not raise substantial concerns of applicability. However, these modalities conveyed the smallest number of studies included. Conversely, the proportions of unclear ratings for ECG and echocardiography studies related to the year when these were performed. For the oldest studies, insufficient data for this assessment is commonly reported. SPECT studies generally rated less well showing a balanced proportion of unclear and high risk of bias in all domains. E-Figure 1 in the Supplement shows this assessment across techniques in an ascending order of risk. Overall quality per type of reference standard is shown in Figure 2.

Performance Estimates

The pooled analysis considering anatomically significant CAD included a total of 2,442 patients for stress ECG, 4,302 for stress echo (with exercise or vasodilator), 2,756 for

CCTA, 4,346 for exercise stress SPECT, 6,551 for exercise & adenosine or dipyridamole stress SPECT, 418 for PET, and 3,393 for stress CMR. Further, the pooled analysis considering functionally significant CAD included 954 for ICA, 1,140 patients for CCTA, 740 for exercise stress SPECT, 709 for PET, and 588 for stress CMR. Some studies evaluated several techniques or technique subgroups simultaneously. Such studies were included as independent entries in more than one pooled analysis per technique.

Table 1 summarizes the performance estimates for every diagnostic technique according to each reference standard. Some techniques had various subcategories typically according to the type of stressor utilized. Some of these subcategories are less commonly used or did not yield adequate information for a summary estimate (e.g. stress echo with dobutamine stress n=30, dobutamine stress SPECT n=2, and dobutamine stress CMR n=2) and were not included in these estimates.

Considering anatomically significant CAD, there were 11 vasodilatory stress echocardiography studies and analysis considering >50% as significant stenosis yielded a sensitivity of 0.75 [0.70, 0.80] and specificity of 0.91 [0.86, 0.94]. These summary estimates were not statistically different from the summary estimates obtained for exercise stress echo (likelihood ratio test *p*-value=0.386) and were consequently pooled together. The summary estimates obtained from 27 dobutamine stress echocardiography studies were 0.81 [0.77, 0.85] for sensitivity and 0.84 [0.81, 0.87] for specificity and given that these estimates were significantly different from exercise stress echocardiography (likelihood ratio test *p*-value=0.012), they were not pooled together but their references can be consulted in the supplementary material.

When anatomically significant CAD was used as reference standard, the LR– of different tests varied from 0.04 to 0.68. The best performance in ruling out CAD was achieved using CCTA and poorest with stress ECG. The LR+ varied from 1.53 to 5.87. The best

performance for ruling in CAD was achieved using PET and the poorest with stress ECG. The LR+ and LR- for dobutamine stress echocardiography subgroup were 8.03 [4.98, 12.95] and 0.27 [0.22, 0.34], respectively (not shown in the tables).

When functionally significant CAD was considered as reference standard, LR– varied from 0.13 to 0.44. CCTA, PET, and stress CMR had the best and similar performance in ruling out significant CAD (–LR=0.13 [0.07, 0.24]), while interestingly, ICA had the poorest. The LR+ of the available techniques varied from 1.97 to 7.10. The poorest performances in ruling-in an abnormal FFR were documented for CCTA (LR+=1.97 [1.28, 3.03]) and ICA (LR+=2.49 [1.47, 4.21]), while functional imaging tests conversely demonstrated the best performance (LR+ range: 3.87-7.1). We could not identify enough robust studies to pool estimates for stress ECG and stress echocardiography.

Effectiveness of non-invasive diagnostic techniques in ruling in/out significant CAD

The Fagan nomogram is a useful tool to graphically apply LRs to a PTP to calculate the post-test probability. A parallel example of its use is depicted in Figure 3, which shows how one can calculate the post-test probabilities after a positive or negative test result starting from any PTP in an individual patient.

The same nomogram can be also utilized backwards so that we can assess the PTP values that will lead to a defined range of post-test probability for each diagnostic method. Therefore, using the data from the meta-analysis, we defined the ranges of PTP of CAD where the diagnostic techniques can confidently rule-in (by driving the post-test probability above 85%) and/or rule-out (by driving the post-test probability below 15%) significant CAD. This was done separately for both anatomically and functionally significant CAD. Such ranges are schematically shown along with their corresponding upper and lower limits in Figure 4 and numerically reported in e-Table 4 in the Supplement.

Finally, based on the obtained data described above, we transformed the PTP table from the 2013 ESC Guidelines on the management of stable coronary artery disease (4) into a supplemental guide that exemplifies how clinicians could implement the resulting estimates of performance in this report in order to select a diagnostic test that confidently rules-in or rules-out CAD (both anatomically and functionally significant CAD) at each patient PTP category (e-Figure 2 panels A and B, respectively).

DISCUSSION

The present study analyzed the evidence on the performance of different diagnostic techniques for the detection of either anatomically or functionally significant CAD. Beyond reporting traditional metrics, we also portrayed their performance as LRs and defined the optimal ranges of PTP for each test where they can reclassify patients from intermediate to either low or high post-test probability of CAD (i.e. rule-out or rule-in, respectively).

From this analysis several main messages can be driven. Stress ECG appears to have very limited diagnostic power to rule-in or rule-out significant CAD. In fact, there was no single PTP value in which stress ECG can both define the diagnosis and exclude it. Moreover, even to confidently rule-out CAD, a very low PTP (≤19% [15, 25]) is needed, while for ruling-in, a PTP ≥80% [76, 83] is required.

As expected, the performance of imaging methods was clearly better than that of stress ECG. However, there appears to be also differences between them. A negative result in CCTA, which conveys a strong LR-, can exclude anatomically defined CAD in nearly all patients independently of their pre-test probability. The performance was clearly poorer when FFR was considered the reference standard as CCTA could only exclude functionally significant CAD at a PTP ≤57% [40, 72]. Correspondingly, the rule-in power, that was

moderate to good when considering ICA as reference, also clearly deteriorated when FFR was used as reference standard.

The functional imaging techniques (PET, CMR, SPECT), which had only moderate power in identifying anatomically significant CAD, performed much better when FFR was used as reference standard. This is in agreement with previous notions and a recently published meta-analysis (9,13). PET and stress CMR demonstrated the best diagnostic performance and offered reasonable range of pre-test probabilities where they could simultaneously rule-out or rule-in functionally significant CAD as shown in Figure 4. However, the comparison between functional imaging techniques must be done cautiously as not enough data was available for stress echocardiography and SPECT studies were older. Furthermore, in more recent studies, referral bias to reference technique is a common phenomenon with established techniques, which typically leads to underestimation of the test specificity. Also, the recent technical advances in were not accounted for as the data was heavily weighted by older studies. Therefore, the previously established tests may underperform in the present analysis.

We also assessed the performance of ICA itself in detecting functionally significant CAD even though it does not classify as a non-invasive test. ICA demonstrated the poorest ruling-out performance of all analyzed techniques when the reference standard was FFR as a PTP ≤27% [24, 31] was needed to rule-out functional CAD. Consistently, the PTP range to rule-in functionally significant CAD was rather modest (≥71% [59, 81]) and only slightly superior to CCTA (≥75% [67, 83]). This behavior fits well with the current recommendation that ICA should be used primarily in patients with high PTP.

Although a pooled evaluation of non-invasive imaging techniques for diagnosing functionally significant CAD has been performed recently, (14) the present study expands the evidence by also considering stress ECG performance, evaluating the competence of ICA

alone in determining functionally significant CAD, conveying the practical ranges of application for the involved diagnostic techniques and parsing the determination of CAD both against anatomical and functional standards. This is timely and relevant considering that anatomical definition of CAD is still widely used in the daily clinical scenario in many healthcare centers around the world, while at the same time acknowledging that FFR indeed represents the currently most adequate reference standard.

Clinical implications

Our clinical conclusions partly differ from those in the current clinical guidelines. For example, in ESC guidelines (4) stress ECG is recommended in patients with lower intermediate PTP (15-65%) of CAD. Our analysis argues against this statement as the practical utility of stress ECG in detecting CAD appears very limited (Figure 4A and e-Figure 2A). However, exercise testing also provides complementary information beyond ECG changes, such as exercise capacity, arrhythmias, hemodynamic response, and symptoms during exercise, which are considered clinically useful. These, however, could not be taken into account in the present analysis.

CCTA has rapidly gained popularity mainly based on its high negative predictive value. This was confirmed in the present analysis by the low LR-, which suggests that a negative result can reliably rule-out anatomic CAD virtually at any level of intermediate pre-test probability (Figures 4A and e-Figure 2A). However, with a high probability of CAD, exclusion of disease is clinically less beneficial because, statistically, most patients will have the disease, and in order to rule-out CAD in one patient, a considerably large number of patients must be investigated. Additionally, the rule-out power decreased when considering FFR as reference. A known limitation of CCTA is low specificity, especially in identifying

functionally significant CAD (53%), and this links to our finding that a PTP ≥75% is required to rule it in (Figure 4B).

Not surprisingly, non-invasive imaging methods that characterize the functional consequences of CAD (rather than the coronary atherosclerotic lesions themselves) perform better when FFR is used as a reference standard and outperform CCTA (Figure 4A vs. 4B). Clearly, every technique has a particular diagnostic performance profile. The techniques focus on different levels of the ischemic cascade including wall motion abnormalities (echocardiography and stress CMR), relative perfusion abnormalities (stress CMR and SPECT), and changes in physiological absolute regional myocardial perfusion (PET).

Out of the functional imaging tests, PET and stress CMR demonstrated good performance with optimal application ranges (for both ruling-in and ruling-out disease) for anatomic and functional CAD. Stress echocardiography and SPECT perfusion imaging performance numbers appeared moderate but direct comparison to other methods must be done cautiously, for the reasons explained above. In addition, as shown in e-Figure 2, the clinical impact of these differences in the utility of the various functional tests is modest although detectable. It is also important to remember that accessibility, simplicity, expertise, personnel, and costs are still important determinants for choosing a given test, and unfortunately, these variables could not be included in this analysis.

Finally, the 2016 update of the stable chest pain guideline, the National Institute for Health and Care Excellence (NICE)(15) has chosen not to include the assessment of PTP and rather recommended CCTA as the first-line diagnostic test and ischemia testing as second step in those with suspected anatomically-relevant CAD. Our analysis does not argue against this approach but we would like to underline that such rationale will depend on the actual prevalence of CAD in the population. The PTP tables currently included in the guidelines are based on reasonably old data while the prevalence of CAD is continuously decreasing. With

low prevalence of CAD the primary first task of imaging may be the accurate exclusion of anatomic CAD, for which CCTA has demonstrated a strong role. The proposed sequential utilization of functional imaging tests may indeed be relevant but it must be kept in mind that the evidence is still limited although prognostic utility and overall safety appears to be excellent.(16)

Limitations

The performance of a given test in different publications varies due to numerous reasons such as population selection and referral bias. Age, gender or participants with history of MI may effect on the estimates of diagnostic accuracy but analyses of these characteristics on a group level may lead to spurious results due to the risk of ecological fallacy bias. We did not have access to individual patient level data or subgroup data that are needed to validly analyze these characteristics. Another potentially important source of variation or bias is study selection based on prior test results or known CAD. Although we excluded case-control studies, we do not know whether study selection was restricted to participants with specific prior test results. The inconsistency between studies lowers the confidence in the summary estimates and future studies should aim to dissect sources of bias and variation.

Furthermore, the present study considers visual analysis alone for the determination of significant CAD through ICA. Advances in ICA evaluation, such as QCA and the implementation of IVUS and OCT(17), could improve identification of hemodynamically-significant lesions. However, clinical practice in many centers currently relies on direct visual ICA evaluation and, therefore, our results on technique performances are likely to be widely applicable. The cutoff of 50% in ICA was used as this was available in all studies. In addition to known pitfalls of ICA, FFR is not without limitation as it is highly dependent on achieving hyperemia through maximal decrease in microvascular resistances.

As the data was available only at the study-level in several reports, we cannot evaluate how the different techniques can assess the extent and severity of the disease, which are important factors in guiding therapies. As there are limited data on direct comparisons between modalities, differences could not be comprehensively tested.

With regard to analyses using FFR as the reference standard, the low number of identified studies did not allow analyzing all modalities. In addition, our summary estimates were vastly derived from single test accuracy studies, providing indirect evidence to compare test modalities. Due to the very low number of comparative studies identified, no consistency check could be performed between direct and indirect summary estimates. Therefore, small differences between techniques and summary estimates should be interpreted cautiously and considered as directional only. CCTA derived FFR has been investigated recently but this method is not yet well standardized and we decided not to include this method in the current analysis. It is also possible that the best diagnostic performance could be achieved when the tests are applied sequentially.(16) The relevance of complementary features in different techniques warrants further investigation. The supplemental technique selection guide (e-Figure 2) was based on the PTP values published in 2013 ESC guidelines and is naturally susceptible to change when updated PTP values are available.

CONCLUSIONS

The various diagnostic modalities have different optimal performance ranges for the detection of anatomically and functionally significant CAD. Stress ECG appears to have limited diagnostic value at any level of pre-test probability. Imaging methods perform generally better but also have different strengths and weaknesses. CCTA performs best against anatomical reference standard and functional tests perform better than CCTA or ICA for functionally significant CAD.

The selection of a diagnostic technique for any given patient to rule-in or rule-out CAD should be based on the optimal PTP range for each test. Using LRs we were able to create individual pre-test ranges for each test to rule-in and/or rule-out anatomic or functional CAD, and these can be used in aiding in the selection of a diagnostic technique for a given patient.

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CONFLICT OF INTEREST STATEMENT

Dr. Ballo, Dr. Juarez-Orozco, and Dr. Rutjes have no competing interests. Dr Knuuti has personal fees from Astra Zeneca outside the submitted work. Dr. Saraste reportspersonal fees from Astra Zeneca, Abbott, Bayer, Actelion, GE, and Novartis, outside the submitted work. Dr. Kolh reports personal fees from Astra Zeneca, B-Braun, Ferrer, outside the submitted work. Dr. Jüni reports grants from Astra Zeneca, grants from Biotronik, grants from Biosensors International, grants from Eli Lilly, grants from The Medicines Company, non-financial support from Astra Zeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company, during the conduct of the study. Dr. Windecker reports grants from Biotronik, Boston Scientific, Bracco Pharmaceutical, Edwards Lifesciences, Medtronic, Terumo Inc, and St Jude Medical, outside the submitted work. Dr. Bax reports grants from Biotronik, Medtronic, Boston Scientific, and Edwards Lifesciences, outside the submitted work. Dr. Wijns reports grants from St Jude now Abbott, Terumo, MicroPort, personal fees from Biotronik, MicroPort, outside the submitted work; and Co-founder of Argonauts Partners; former non-executive Board member of Genae and Cardio3BioSciences (now Celyad).

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FIGURE LEGENDS

Figure 1. Study search and selection flow chart.

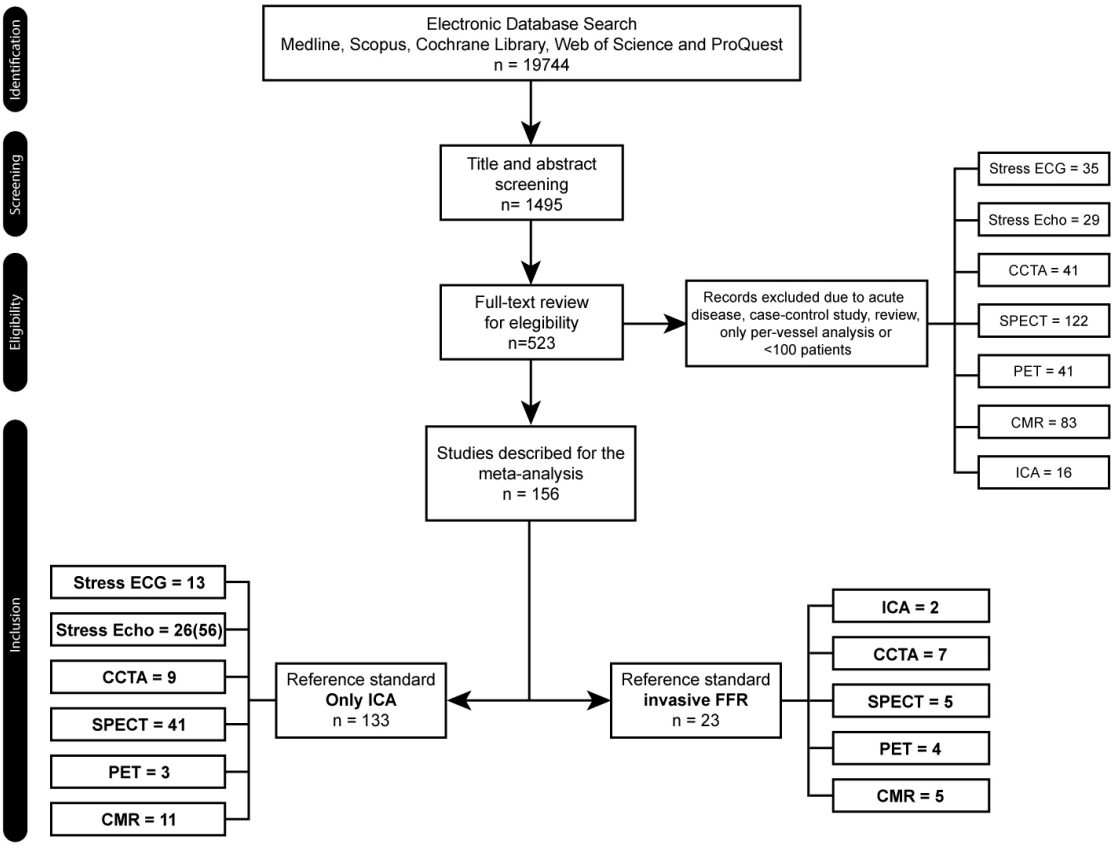


Figure 2. QUADAS assessment summary by type of reference standard for significant CAD.

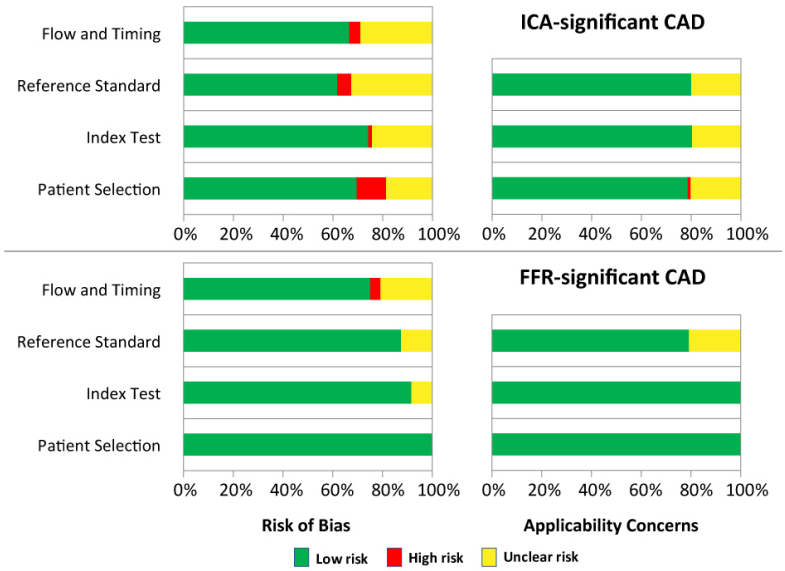


Figure 3. Fagan Nomogram. A hypothetical patient with a calculated **pre-test probability of CAD of 56%** (left-sided scales in panels A and B) undergoes: a stress ECG, CCTA or PET when **anatomically** significant CAD is used as the reference standard (panel **A**), and SPECT, CCTA or PET when functionally significant CAD is used as the reference (panel **B**). In the middle scales, LR+ and LR- are identified and straight lines are drawn between the left and middle scales, and extrapolated to reach the right-sided scales. **In the right-sided scales** of both panels (A and B), **the post-test probability** of a positive and negative test result can be read. The grey bars represents the range of post-test probability in which CAD cannot confidently ruled-in or ruled-out (post-test probability 15-85%). Notice that in panel **A**, stress ECG cannot rule-in or –out but the other two imaging tests can, while in panel **B**, SPECT cannot rule-in or –out, CCTA can only rule-out, and PET can do both.

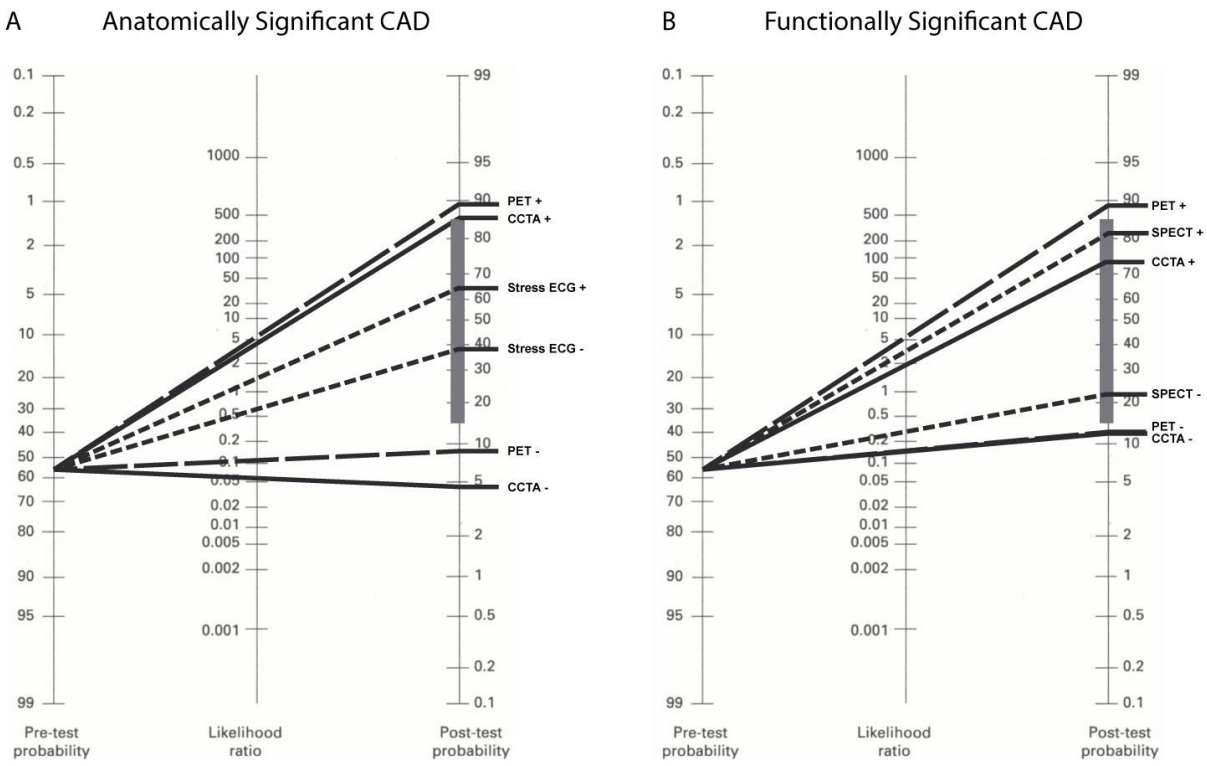
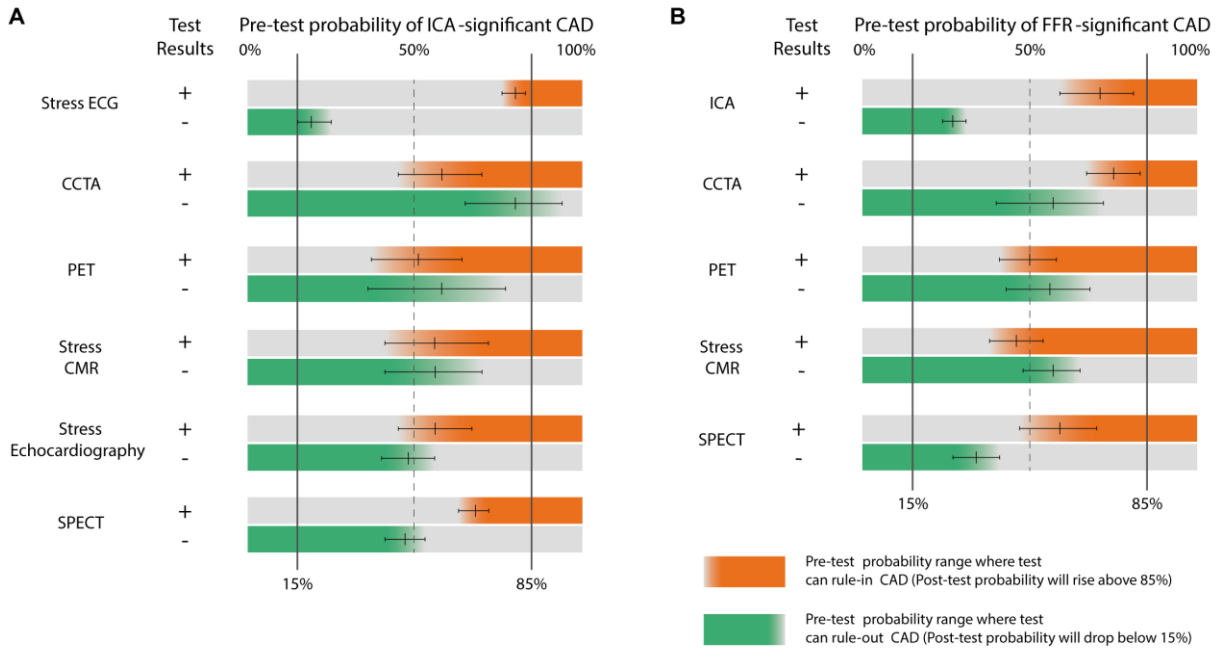


Figure 4. Ranges of clinical pre-test probability in which each single positive test will confidently rule-in (in ORANGE) the presence of significant CAD or, conversely a negative test will confidently rule-out (in GREEN) based on the LR values of the test. **Panel A** shows these ranges when the reference standard is visually significant stenosis in ICA, while **Panel B** shows the ranges when abnormal FFR is the reference standard. The crosshairs mark the mean value and the gradient-colored areas contain their 95% CIs. The results are based on the criteria that disease is confidently ruled-out when the post-test probability is <15% and ruled-in when it is >85%. The numeric values can be consulted in Supplementary e-Table 4.



TABLES

Table 1. The performance of different tests for anatomically (left panel) and functionally significant CAD (right panel). Note: ICA itself was used as a reference standard for the left panel estimates but was included as a technique when FFR was used as the reference. Not every test had enough data using FFR as reference.

Anatomically Significant CAD					Functionally Significant CAD				
Test	**Sensitivity [95%CI]**	**Specificity [95%CI]**	**+LR [95%CI]**	**-LR [95%CI]**	**Test**	**Sensitivity [95%CI]**	**Specificity [95%CI]**	**+LR [95%CI]**	**-LR [95%CI]**
					ICA	68% [60, 75]	73% [55, 86]	2.49 [1.47, 4.21]	0.44 [0.36, 0.54]
Stress ECG	58% [46, 69]	62% [54, 69]	1.53 [1.21, 1.94]	0.68 [0.49, 0.93]					
Stress Echo	85% [80, 89]	82% [72, 89]	4.67 [2.95, 7.41]	0.18 [0.13, 0.25]					
CCTA	97% [93, 99]	78% [67, 86]	4.44 [2.64, 7.45]	0.04 [0.01, 0.09]	**CCTA**	93% [89, 96]	53% [37, 68]	1.97 [1.28, 3.03]	0.13 [0.06, 0.25]
SPECT	87% [83, 90]	70% [63, 76]	2.88 [2.33, 3.56]	0.19 [0.15, 0.24]	**SPECT**	73% [62, 82]	83% [71, 90]	4.21 [2.62, 6.76]	0.33 [0.24, 0.46]
PET	90% [78, 96]	85% [78, 90]	5.87 [3.40, 10.15]	0.12 [0.05, 0.29]	**PET**	89% [82, 93]	85% [81, 88]	6.04 [4.29, 8.51]	0.13 [0.08, 0.22]
Stress CMR	90% [83, 94]	80% [69, 88]	4.54 [2.37, 8.72]	0.13 [0.07, 0.24]	**Stress CMR**	89% [85, 92]	87% [83, 91]	7.10 [5.07, 9.95]	0.13 [0.09, 0.18]

Abbreviations: CI, confidence intervals; CMR, stress cardiac magnetic resonance; CCTA, computed tomography; ECG, electrocardiogram; ICA, invasive coronary angiography; LR, likelihood ratio; PET, positron emission tomography; SPECT, single photon emission computed tomography (Exercise stress SPECT with or without Dipyridamole or Adenosine); Stress Echo, exercise stress echocardiography

ONLINE SUPPLEMENTARY MATERIAL

The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: A meta-analysis focused on post-test disease likelihood

Table S1. MOOSE Checklist.

Items	Recommendation	Described in element or page
Reporting of background should include		
1	Problem definition	6
2	Hypothesis statement	6
3	Description of study outcome(s)	8
4	Type of exposure or intervention used (non-invasive techniques)	6-7
5	Type of study designs used	7
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7-8
8	Search strategy, including time period included in the synthesis and key words	7
9	Effort to include all available studies, including contact with authors	8
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	7
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Fig 1 and E-table 2
14	Method of addressing articles published in languages other than English (na)	7
15	Method of handling abstracts and unpublished studies	7
16	Description of any contact with authors	7-8
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	9
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7, Fig 2
22	Assessment of heterogeneity	8-9, 10
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	Fig 1-5, E-table 1,3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 4, Table 1

26	Table giving descriptive information for each study included	e-Table 2
27	Results of sensitivity testing (eg, subgroup analysis)	11
28	Indication of statistical uncertainty of findings	11, 16
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	NA
30	Justification for exclusion (eg, exclusion of non-English language citations)	Fig 1
31	Assessment of quality of included studies	Fig 2 and e-Fig 1
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	19, Fig 5
34	Guidelines for future research	18
35	Disclosure of funding source	20

Table S2. Electronic search terms

Search string	(("Electrocardiography"[Mesh] OR stress ECG OR stress electrocardiography) OR ("Echocardiography, Stress"[Mesh] OR stress echocardio*) OR ("Computed Tomography Angiography"[Mesh] OR coronary computed tomography angiography OR CCTA OR coronary angiotomography OR MDCT) OR ("Tomography, Emission-Computed, Single-Photon"[Mesh] OR SPECT OR SPET) OR ("Positron-Emission Tomography"[Mesh] OR PET) OR ("Magnetic Resonance Imaging"[Mesh] OR cardiac magnetic resonance OR CMR) OR ("Coronary Angiography"[Mesh] OR invasive coronary angiography OR ICA) OR ("Fractional Flow Reserve, Myocardial"[Mesh] OR FFR)) AND (("Coronary Artery Disease"[Mesh] OR stable coronary artery disease OR stable CAD OR stable angina)) AND ((diagnosis OR performance))
Filter	Human Studies

Table S3. Characteristics of included studies on diagnosis of angiographically and functionally significant CAD. The full reference list in included after the table.

Study	Year	Reference	No. of patients	Mean Age	Women (%)	Prior MI (%)	Sensitivity (%)	Specificity (%)	Prevalence of CAD (%)	Technique
Amanuallah[1]	1997	ICA	222	71	46	0	92.9	72.6	76.7	SPECT Vasodilator
Anthopoulos[2]	1996	ICA	120	75	40	40	86.5	83.9	74.2	Echo Dobutamine
Bateman[3]	2006	ICA	112	67	54	25	87.1	92.9	62.5	PET
Beleslin[4]	1994	ICA	136	50	14.7	56.6	87.4	82.4	87.5	Echo Exercise
Beleslin[4]	1994	ICA	136	50	14.7	56.6	74	94.1	87.5	Echo Vasodilator
Beleslin[4]	1994	ICA	136	50	14.7	56.6	82.4	76.5	87.5	Echo Dobutamine
Berman[5]	2006	ICA	785	N/A	N/A	0	90.6	55.5	70.7	SPECT Vasodilator
Berman[5]	2006	ICA	290	N/A	N/A	0	82.7	86.2	77.6	SPECT Vasodilator
Berman[5]	2006	ICA	365	NA	NA	0	91.3	55.6	75.3	SPECT Exercise
Bernhardt[6]	2009	ICA	823	64	24	N/A	87.5	82.6	38	Stress CMR
Bettencourt[7]	2013	FFR	101	62	23	0	100	61.4	43.6	CCTA
Bettencourt[7]	2013	FFR	101	62	34	0	88.6	87.7	43.6	Stress CMR
Beygui [8]	2000	ICA	179	61	16.2	4.5	50.8	62.3	36.3	Stress ECG
Bokhari[9]	2008	ICA	218	56	31	0	81.1	78.7	65.6	SPECT Exercise
Budoff[10]	2008	ICA	227	57	41	0	94.5	82.6	24.2	CCTA
Celutkine[11]	2012	ICA	151	62	41.1	0	83	92.9	35.1	Echo Dobutamine
Chae[12]	1993	ICA	243	62	100	42	71.2	65	67.1	SPECT Exercise
Chae [12]	1993	ICA	243	65	100	42	25.1	38.2	72	Stress ECG
Chen [13]	2013	ICA	151	65	40	0	92.3	95.7	35.9	Stress CMR
Christian[14]	1992	ICA	688	63	23	42	91.8	39.4	81.3	SPECT Exercise
Crouse[15]	1991	ICA	228	62	32.9	0	97.1	64.2	76.8	Echo Exercise
Danad[16]	2014	FFR	281	61	32	0	89.3	84	39.9	PET
Danad[17]	2013	FFR	120	58	49	0	75	83.1	40.8	PET
Daou[18]	2002	ICA	338	56	17	60	63	76.7	78.4	SPECT Exercise
Daou [18]	2002	ICA	338	59	8.3	59.8	46.9	63.8	76.3	Stress ECG
DeFACTO study[19]	2012	FFR	252	62.9	29.4	6	83.9	41.7	54.4	CCTA
DISCOVER-FLOW[20]	2011	FFR	103	62.7	28	17	94.8	24.4	56.3	CCTA

Dolan[21]	2001	ICA	112	61	45	22	71.4	81	81.3	Echo Dobutamine
Dondi[22]	2004	ICA	130	63.2	40	0	96.3	72.7	83.1	SPECT Exercise
Doyle[23]	2003	ICA	184	59	100	N/A	61.5	82.3	14.1	SPECT Vasodilator
Ebersberger[24]	2013	FFR	116	63	39	0	85	86.8	34.5	Stress CMR
Elhendy[25]	1996	ICA	133	60	23.5	N/A	78.4	86.4	83.5	Echo Dobutamine
Elhendy[26]	1998	ICA	290	58	30.3	N/A	72.2	85.5	76.2	Echo Dobutamine
Elhendy[27]	1998	ICA	295	N/A	N/A	N/A	75	86.8	77	Echo Dobutamine
Emmett[28]	2002	ICA	100	60	23	0	88.6	63.3	70	SPECT Exercise
EVINCI-study[29]	2015	ICA	293	60.9	39	0	73	66.8	34	SPECT Vasodilator
EVINCI-study[29]	2015	ICA	475	60.9	39	0	90.7	91.9	29.4	CCTA
Ferrara[30]	1991	ICA	109	62	37.7	N/A	78.9	99	82.6	Echo Vasodilator
Fragasso[31]	1999	ICA	101	61	45.5	0	61.4	90.9	56.4	Echo Vasodilator
Fragasso[31]	1999	ICA	101	61	45.5	0	87.7	79.6	56.4	Echo Dobutamine
Gallowitsch[32]	1998	ICA	107	64	46	39.3	94.3	90.7	49.5	SPECT Vasodilator
Greenwood[33]	2012	ICA	752	65	37	0	86.5	83.4	39.4	Stress CMR
Geleijnse[34]	1995	ICA	223	58	31.4	0	72	78.8	64.1	Echo Dobutamine
Gentile[35]	2001	ICA	132	70	31	0	93.5	54.2	81.8	SPECT Vasodilator
Gentile [35]	2001	ICA	132	70	31.8	0	85.2	58.3	81.8	Stress ECG
Go[36]	1990	ICA	202	NA	NA	47	93.4	78	75.3	PET
Gonzalez[37]	2005	ICA	145	60	32	36	87.2	57.1	80.5	SPECT Vasodilator
Greenwood[33]	2012	ICA	752	60	37	0	66.5	82.7	39.4	SPECT Vasodilator
Groothuis[38]	2013	ICA	192	56	51	0	85.5	81.3	35.9	Stress CMR
Groutars[39]	2003	ICA	123	63	27.6	52	96.9	59.3	78.1	SPECT Exercise
Gueret[40]	2013	ICA	746	61	29	20	91	50	34.7	CCTA
Hamasaki [41]	1996	ICA	125	64	24	0	83	65.4	37.6	Stress ECG
Hambye[42]	2004	ICA	100	63	52	43	73.3	78.6	86	SPECT Vasodilator
Hanekom[43]	2007	ICA	150	66	33	19	91	52.5	59.3	Echo Dobutamine
Hecht[44]	1993	ICA	180	56	13.9	N/A	93.4	86.1	76.1	Echo Exercise
Hecht[45]	1993	ICA	136	59	11	N/A	83	90.5	69.1	Echo Exercise
Hecht [46]	1990	ICA	116	58	19.8	42.2	51.5	64.6	58.6	Stress ECG

Hennessy[47]	1997	ICA	317	60	27.8	42.2	85.4	60.5	86.4	Echo Dobutamine
Hennessy[48]	1998	ICA	218	62	100	47.7	49	85	90.8	Echo Dobutamine
Hida[49]	2009	ICA	119	68	33	0	51.6	87.7	52.1	SPECT Vasodilator
Ho[50]	1997	ICA	223	58	19.3	N/A	93.8	78.7	72.7	Echo Dobutamine
Hoffmann[51]	1996	ICA	150	46	20.5	0	75.8	87.3	63.3	Echo Dobutamine
Hoffmann[52]	1999	ICA	283	56	33.3	0	72.1	78	64.7	Echo Dobutamine
Hung[53]	2006	ICA	126	66	30	8.7	92.6	64.4	64.3	SPECT Vasodilator
Ishida[54]	2003	ICA	104	66	22	0	89.6	85.2	74	Stress CMR
Jakljevic[55]	2012	FFR	154	65	NA	0	87.0	67.0	35.1	SPECT Vasodilator
Jeetley[56]	2006	ICA	123	62	46	33	85.9	50	69.1	SPECT Vasodilator
Johansen[57]	2005	ICA	357	57	63	0	74.6	79.2	35.3	SPECT Vasodilator
Joutsiniemi[58]	2014	FFR	104	64	62	0	94.6	86.6	35.6	PET
Kajander[59]	2010	FFR	107	63	45	0	95	86.6	37.4	CCTA
Kajander[59]	2010	ICA	104	63	45	0	94.7	90.9	36.5	PET
Kajinami[60]	1995	ICA	251	56	30.7	N/A	73.7	75.4	53	Stress ECG
Kajinami[60]	1995	ICA	251	56	32	0	82.7	59.3	53	SPECT Exercise
Kang[61]	2013	FFR	700	62	30	0	71.4	60.6	38	ICA
Khattar[62]	1998	ICA	100	62	30	28	67.6	80.8	74	Echo Dobutamine
Khattar [62]	1998	ICA	100	62	30	70	69.6	40.9	56	Stress ECG
Ko[63]	2014	FFR	115	64	24	10	94.4	54.3	78.3	CCTA
Koskinen[64]	1987	ICA	100	57	44.7	N/A	63.3	80	90	Stress ECG
Latcham[65]	1995	ICA	106	63	39.3	N/A	74.4	65	81.1	Echo Dobutamine
Lipiec[66]	2008	ICA	103	58	36	50	92.4	54.2	76.7	SPECT Vasodilator
Mahmarian[67]	1990	ICA	360	56	26	22	86.9	86.7	74.7	SPECT Exercise
Mairesse[68]	1994	ICA	129	56	30.2	0	75.9	84.8	64.3	Echo Dobutamine
Mairesse [68]	1994	ICA	129	56	26.4	N/A	42.2	82.6	64.3	Stress ECG
Manka[69]	2015	FFR	150	63	30	0	84.7	90.8	56.7	Stress CMR
Manka[70]	2012	FFR	120	64	25	0	89.9	82.4	57.5	Stress CMR
Marcovitz[71]	1992	ICA	141	60	40.4	10.6	96.3	65.6	77.3	Echo Dobutamine
Marwick[72]	1992	ICA	150	57	21.3	N/A	84.2	86.1	76	Echo Exercise

Marwick[73]	1995	ICA	161	60	100	0	79.7	81.4	36.7	Echo Exercise
Marwick[74]	1995	ICA	147	58	40.8	0	71	90.6	42.2	Echo Exercise
Marwick[75]	1993	ICA	217	58	28.1	0	71.8	82.7	65.4	Echo Dobutamine
Meijboom[76]	2007	ICA	104	58	27	0	100	75	84.6	CCTA
Meijboom[77]	2007	ICA	123	62	100	0	100	75	51.2	CCTA
Meijboom[77]	2007	ICA	279	58	0	0	98.9	89.9	68.1	CCTA
Meijboom[78]	2008	ICA	360	60	32	0	99.2	64	68	CCTA
Merkle[79]	2007	ICA	228	61	21	0	93	85.7	75.4	Stress CMR
Meuwissen[80]	2002	FFR	151	60	29	38	69.2	76.7	34.4	SPECT Vasodilator
Michaelides [81]	1999	ICA	245	52	11	0	65.9	88.2	86.1	Stress ECG
Miller[82]	1997	ICA	243	63	1.2	34.7	91.1	27.5	83.5	SPECT Vasodilator
Miller[83]	2008	ICA	291	59	26	0	87.4	89.6	59.8	CCTA
Miyazono[84]	1998	ICA	112	66	27.7	N/A	74.2	90	55.4	Echo Vasodilator
Mohiuddin[85]	1996	ICA	202	58	41	N/A	90	85.7	79.2	SPECT Vasodilator
Motwani[86]	2012	ICA	111	61	26	12	93.8	66.7	87.3	Stress CMR
Mouden[87]	2014	FFR	100	66	36	NA	60	76.25	20	SPECT Vasodilator
Nagel[88]	1999	ICA	163	60	29.3	0	74.3	81.5	66.9	Echo Dobutamine
Nallamothu[89]	1995	ICA	321	57	0.33	0	80.9	68.5	83.2	SPECT Exercise
Nallamothu [89]	1995	ICA	321	57	24.9	N/A	46.2	59.5	76.9	Stress ECG
Nedelikovic[90]	2006	ICA	117	54	22	27.4	92.8	91.7	59	Echo Vasodilator
Nedelikovic[90]	2006	ICA	117	54	22	27.4	89.9	87.5	59	Echo Dobutamine
Nedelikovic[90]	2006	ICA	117	54	22	27.4	95.7	91.67	59	Echo Dobutamine
Norgaard[91]	2014	FFR	254	64	36	2	93.8	33.9	31.5	CCTA
Norgaard[91]	2014	FFR	254	62	36	2	63.8	82.8	31.5	ICA
Ostojic[92]	1994	ICA	150	51	16.7	50.7	71	89.5	87.3	Echo Vasodilator
Ostojic[92]	1994	ICA	150	51	16.7	50.7	74.8	79	87.3	Echo Dobutamine
PACIFIC trial[93]	2016	FFR	206	58	36	0	57.0	93.8	45.1	SPECT Vasodilator
PACIFIC trial[93]	2016	FFR	208	58	36	0	90.2	60.3	44.2	CCTA
PACIFIC trial[93]	2016	FFR	204	58	36	0	86.7	84.2	44.1	PET
Parodi[94]	1999	ICA	101	55	19.8	0	77.5	76.2	79.2	Echo Vasodilator

Pasierski[95]	2001	ICA	248	53	33	0	81.9	96.2	46.8	Echo Exercise
Pasierski[95]	2001	ICA	248	53	33	0	74.1	97.7	46.8	Echo Dobutamine
Peteiro[96]	2012	ICA	116	61	15.5	40.5	84	63.4	64.7	Echo Exercise
Picano[97]	1989	ICA	374	54	23.4	36	72.7	87.8	80.2	Echo Vasodilator
Picano[98]	1993	ICA	178	58	15.6	0	72.3	95.8	73	Echo Vasodilator
Pilz[99]	2006	ICA	171	62	37	28.1	96.5	82.8	66.1	Stress CMR
Pingitore[100]	1996	ICA	110	60	16.7	N/A	81.5	94.4	83.6	Echo Vasodilator
Pingitore[100]	1996	ICA	110	60	16.7	30	94.6	88.9	83.6	Echo Dobutamine
Porter[101]	2011	ICA	100	62	40	29	59.6	72.9	52	Echo Vasodilator
Poyraz[102]	2014	ICA	281	62.6	61.2	0	86	94	27	SPECT Vasodilator
Psirropoulos[103]	2002	ICA	606	54	52	19.8	93	43.8	19.6	SPECT Exercise
Quinones[104]	1992	ICA	112	57	33.2	N/A	74.4	88.5	76.8	Echo Exercise
Roger[105]	1995	ICA	127	N/A	N/A	N/A	87.9	70	84.3	Echo Exercise
Roger[106]	1997	ICA	340	65	28.2	0	78.2	40.9	74.1	Echo Exercise
San Roman[107]	1996	ICA	102	62	43	0	77.8	97.4	61.8	Echo Vasodilator
San Roman[108]	1998	ICA	102	64	51	0	81.8	94.4	64.7	Echo Vasodilator
San Roman[107]	1996	ICA	102	62	43	0	77.8	94.9	61.8	Echo Dobutamine
San Roman[108]	1998	ICA	102	64	51	0	78.8	88.9	64.7	Echo Dobutamine
Santana Boada[109]	1998	ICA	163	60	38	0	91.7	89.6	58.9	SPECT Vasodilator
Santana-Boado [109]	1998	ICA	163	60	38.7	0	66.7	70.7	49.7	Stress ECG
Schaap [110]	2013	FFR	129	63	35	0	79.7	90.8	49.6	SPECT Vasodilator
Schwitter[111]	2013	ICA	425	61	33	27	59.2	72.2	48.5	SPECT Vasodilator
Schwitter[111]	2013	ICA	533	60	27	27	75.2	58.9	48.5	Stress CMR
Severi[112]	1994	ICA	429	55	28.4	0	74.8	89.6	57.3	Echo Vasodilator
Shabestari[113]	2007	ICA	143	63	28	0	96.3	57.1	75.5	CCTA
Sharples[114]	2007	ICA	224	NA	NA	23	87.3	60.8	68.3	SPECT Vasodilator
Sharples[114]	2007	ICA	226	62	32	31	74	72.7	75.2	Stress CMR
Shelley[115]	2003	ICA	108	70	NA	0	94	79	59.3	SPECT Vasodilator
Shirai[116]	2002	ICA	603	63	3	31	44.7	96.5	39.3	SPECT Exercise
Slomka[117]	2006	ICA	174	63	33	0	83.9	81.1	78.7	SPECT Vasodilator

Smart[118]	2000	ICA	386	61	34.5	N/A	85	86.8	72.5	Echo Dobutamine
Tadehara[119]	2008	ICA	101	72.1	48	19.7	93	70	53.4	SPECT Vasodilator
Takase[120]	2004	ICA	102	66	17	44.1	93.4	84.6	74.5	Stress CMR
Takeuchi[121]	1993	ICA	120	63	25.8	N/A	85.1	93.5	61.7	Echo Dobutamine
Thompson[122]	2005	ICA	116	60	30	0	86.4	78.6	75.9	SPECT Vasodilator
Watkins[123]	2009	FFR	101	60	28	24	94.9	91.3	77.2	Stress CMR
Wolak[124]	2008	ICA	114	65	100	0	79.7	73.3	60.5	SPECT Vasodilator
Wu[125]	2009	ICA	218	64	38	2.8	94.6	62.5	59.6	SPECT Vasodilator
Yoon[126]	2009	ICA	344	63.3	63	0	87	34	63.7	SPECT Vasodilator

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Figure S1. QUADAS assessment summary per diagnostic technique for ICA- and FFR-significant CAD

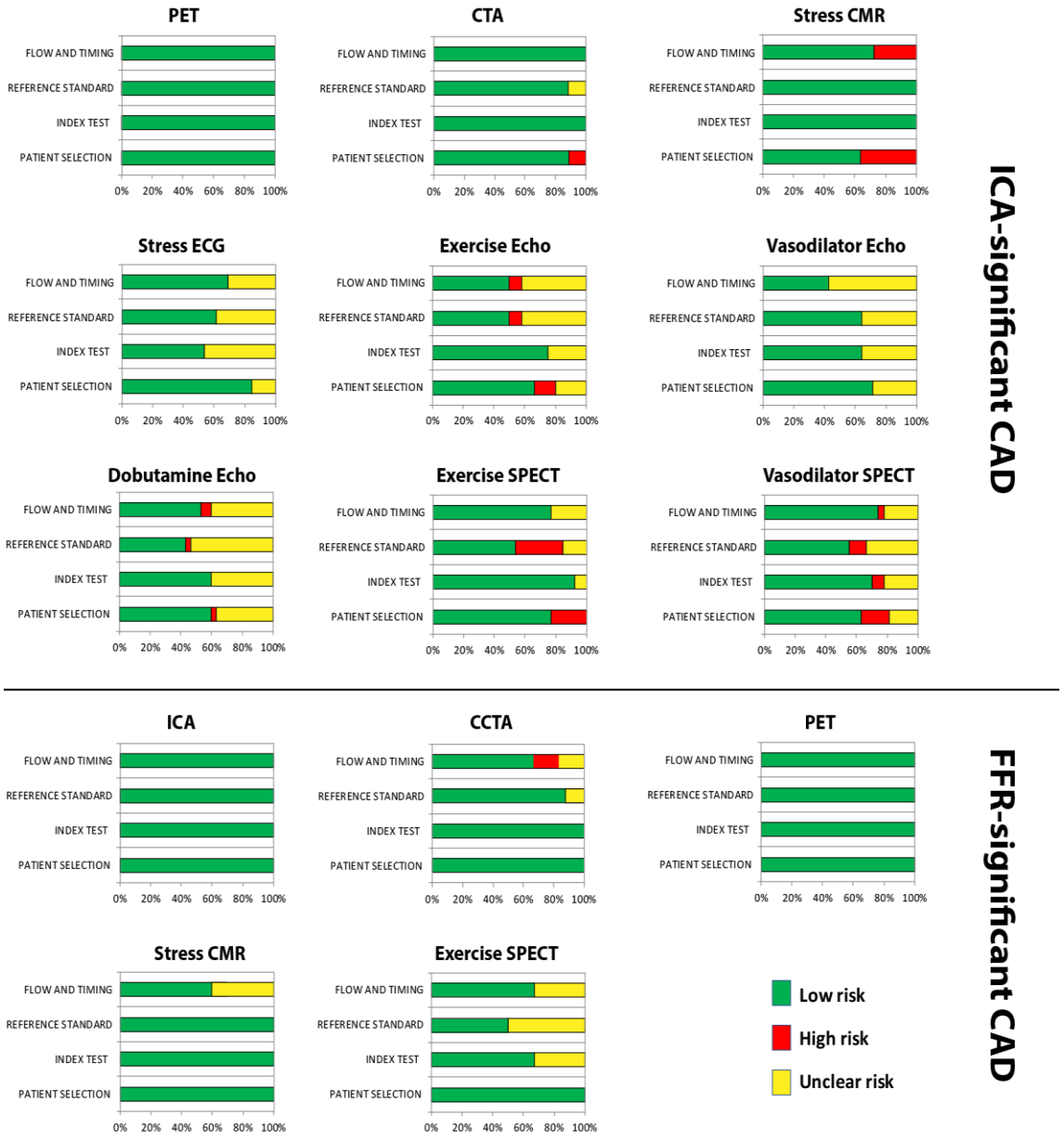

Table S4. Ranges of pre-test probability where the diagnostic techniques can confidently rule-in and rule-out anatomically or functionally significant CAD

Pre-test probability to rule-in or rule-out Anatomically Significant CAD		
	Prob. to Rule-Out [95%CIs]	**Prob. to Rule-In [95%CIs]**
Stress ECG	≤19 [15, 25]	≥80 [76, 83]
CCTA	≤80 [65, 94]	≥58 [45, 70]
PET	≤58 [36, 77]	≥51 [37, 64]
Stress CMR	≤56 [41, 70]	≥56 [41, 72]
Stress ECHO	≤48 [40, 56]	≥56 [45, 67]
SPECT	≤47 [41, 53]	≥68 [63, 72]
Pre-test probability to rule-in or rule-out Functionally Significant CAD		
	Prob. to Rule-Out [95%CIs]	**Prob. to Rule-In [95%CIs]**
ICA	≤27 [24, 31]	≥71 [59, 81]
CCTA	≤57 [40, 72]	≥75 [67, 83]
PET	≤56 [43, 68]	≥50 [41, 58]
Stress CMR	≤57 [48, 65]	≥46 [38, 54]
SPECT	≤34 [27, 41]	≥59 [47, 70]

Figure S2. Simple guide to help selection of a test to detect stable CAD based on age, sex and symptoms. Table A shows the selection of a test to detect anatomic ICA-defined CAD and table B, FFR-defined CAD. **Examples:** In a 55-year old male patient with atypical angina CCTA, SPECT, PET and stress CMR can reliably rule-out anatomically significant CAD but stress ECG or stress echocardiography cannot (**A**). To assess the performance of imaging tests to detect functionally significant CAD (assessed by FFR) in the same patient (**B**) one can see that PET and stress CMR results can both rule-out and rule-in significant CAD while CCTA can only confidently rule-out if a negative result is documented. ICA and SPECT are not recommended tests in this patient. No data about Stress ECG and stress echocardiography was available against FFR. Note: the guide table is based on the 2013 ESC SCAD Guidelines and may be subject to change when the pre-test probabilities are updated. Abbreviations: SCAD, stable coronary artery disease; CMR, stress cardiac magnetic resonance; CT, coronary computed tomography angiography; ECG, stress electrocardiogram; Echo, stress echocardiogram; FFR, fractional flow reserve; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single photon emission computed tomography.